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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/439,429	11/15/99	POWER	C 3045.00004

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1635	3

DATE MAILED: 05/10/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

U.S. G.P.O. 1999-460-693

Office Action Summary

Application No.	Applicant(s)
09/439,429	POWER et al.
Examiner	**Group Art Unit**
Janet Epps	1635

[X] Responsive to communication(s) filed on *Nov 15, 1999*

[ ] This action is **FINAL.**

[ ] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

[X] Claim(s) *3-16* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

[ ] Claim(s) _____ is/are allowed.

[X] Claim(s) *3-16* is/are rejected.

[ ] Claim(s) _____ is/are objected to.

[ ] Claims _____ are subject to restriction or election requirement.

Application Papers

[ ] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

[ ] The drawing(s) filed on _____ is/are objected to by the Examiner.

[ ] The proposed drawing correction, filed on _____ is [ ] approved [ ] disapproved.

[ ] The specification is objected to by the Examiner.

[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

[ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

[ ] All [ ] Some* [X] None of the CERTIFIED copies of the priority documents have been

[ ] received.

[ ] received in Application No. (Series Code/Serial Number) _____.

[ ] received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

[ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

[X] Notice of References Cited, PTO-892

[ ] Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

[ ] Interview Summary, PTO-413

[X] Notice of Draftsperson's Patent Drawing Review, PTO-948

[ ] Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Arguments

1. Applicant's arguments filed 11-15-99 regarding the rejection of claims 3-4 and 7-10 under 35 USC 112 first paragraph have been fully considered but they are not persuasive. Response to the arguments are found in the modified rejections of these claims below.

Sequence Information

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The applicant did not submit a Sequence Listing as a paper copy or in CRF for this application.

A complete response to this office action requires that Applicants comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 5-6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 6,046,319. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: a synthetic and nuclease resistant oligonucleotide having a nucleotide sequence as set forth in SEQ ID NO: 4 and SEQ ID NO:6.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 5, 9, and 11-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 5 and 9 provide for the use of an antisense oligonucleotide and a pharmaceutical composition, respectively, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 5 and 9 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claims 5, and 11-12 recites "targeting exon sequences flanking donor splice sites thereby regulating expression of TNF-a", this phrase is vague and indefinite since it is unclear which "exon sequences flanking donor splice sites" Applicants are referring to.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 3-4, and 7-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth below in the following rejection.

10. Claim 10, and 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting the expression of TNF-alpha *in vitro*, does not reasonably provide enablement for modulating, which includes for enhancing and inhibiting, the expression of TNF-alpha, *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 3-4, and 7-16 are drawn to pharmaceutical compositions comprising a synthetic nuclease resistant antisense oligonucleotide, compositions comprising antisense oligonucleotides which selectively modulate human tumor necrosis factor alpha, and methods of modulating the expression of human tumor necrosis factor in a mammal.

The specification as filed only disclose that the oligonucleotides of the instant invention have the ability to reduce the expression of TNF-alpha, there are no examples teaching how to use these oligonucleotides to enhance the expression of TNF-alpha expression, therefore the specification as filed does not teach how to modulate the expression of TNF-alpha comprising the administration of an antisense oligonucleotide.

The compositions and methods of use of antisense oligonucleotides recited in these claims implies *in vivo* applicability for enablement purposes. There are no general guidelines for successful *in vivo* delivery of antisense/ribozyme compounds currently known in the art, wherein said method specifically delivers the antisense to the site of need and produces the desired secondary result associated with the function of antisense compound, nor are such guidelines provided in the specification as filed. The current state of the art teaches that the behavior of antisense oligonucleotides *in vivo* and *in vitro* is unpredictable. Crooke (1998), states that "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate". Crooke goes on to teach that variations in cellular uptake and distribution of antisense oligonucleotides are influenced by a variety of factors: length of oligonucleotide, modifications, sequence of oligonucleotide and cell type. Crooke also describes several "non-antisense effects", for example phosphorothioate modified oligonucleotides tend to bind to many proteins, protein binding in general by oligonucleotides may influence cell uptake, distribution, metabolism and excretion. Such protein binding may produce effects that can be mistakenly interpreted as antisense activity, and such binding may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may interact with other biological molecules, such as lipids, or carbohydrates, and such interactions, like those with proteins , will be influenced by the chemical class of oligonucleotide studied (Crooke, 1998; p. 3). Crooke clearly teaches that there is a significant level of factors which influence the behavior of antisense based compounds thereby rendering the activity of antisense compounds unpredictable, and thus much experimentation is required to screen multiple antisense compounds to determine not only their efficacy *in vitro* but also *in vivo.*

Branch (1998) also teach that "the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected mechanism." In addition, Branch teaches that the successful delivery of antisense/ribozymes to their specified target *in vivo* is unpredictable, the internal structures of the targeted RNAs and their association with cellular proteins can render target sites totally unaccessible *in vivo*. Antisense therapy is a highly unpredictable and field and the skill in the art is high.

Both Branch and Crooke teach that the behavior of antisense based pharmaceuticals are unpredictable, therefore claims to antisense based pharmaceuticals and methods of treating diseases by the administration of said pharmaceuticals are subject to the question of enablement due to the high level of unpredictability in the antisense art.

Therefore, the specification does not describe the pharmaceutical composition comprising antisense oligonucleotides targeting human tumor necrosis factor alpha, and methods of use of said compositions recited in these claims in a sufficient manner so as to enable one of ordinary skill in the art to practice the present invention without undue experimentation. These conclusions are based upon the known unpredictability regarding the delivery of antisense *in vivo* and further with secondary effects such as treating a disease associated with the expression of human tumor necrosis factor alpha, and the lack of guidance in the specification as filed in this regard.

The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that a single gene is inhibited and the desired secondary effect (treating a patient with a disease associated with the expression of human tumor necrosis factor alpha) is obtained. The specification as filed provides no specific

guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps whose telephone number is (703) 308-8883. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax number for this group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

ROBERT A. SCHWARTZMAN
PATENT EXAMINER

Janet L. Epps, Ph.D.

May 8, 2000